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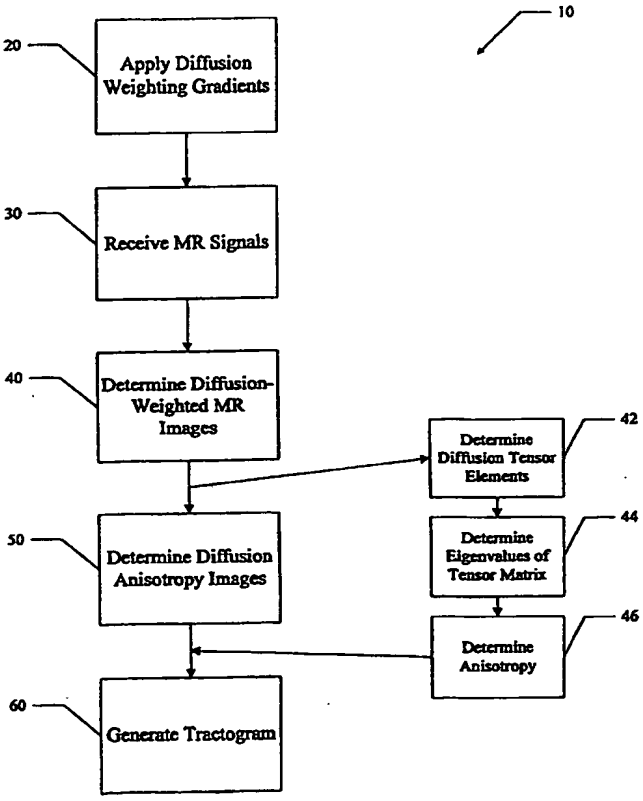

(57) Abstract: Methods and systems for visualizing white-matter tracts in the central nervous system, including the brain and spine. At least two sets of diffusion-weighted magnetic resonance (MR) images are acquired using a fast imaging pulse sequence, such as echo planar imaging, fast spin echo, or a combination of the two. The diffusion tensor anisotropy elements at each voxel in the image are calculated using a least-squares algorithm. A three-dimensional diffusion anisotropy image is obtained either directly from the three-dimensional diffusion-weighted MR images, or by reformatting the two-dimensional multi-slice MR images acquired in an interleaved fashion. A tractogram that highlights the white-matter tracts is produced at a preferred angle within a selected slab using a maximum intensity projection algorithm.

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APPLICATION FOR UNITED STATES LETTERS PATENT

for

METHODS AND SYSTEMS FOR GENERATING TRACTOGRAMS

by

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BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the field of locating fiber tracts in a nervous system. More particularly, it concerns methods and systems for generating brain and spinal tractograms using diffusion-weighted magnetic resonance imaging.

2. Description of Related Art

The human central nervous system is a network of communications established by fiber tracts for the nerve cells to emit and receive signals. Exploring the neuronal connectivity by tracing the fiber tracts may provide valuable information to understand nervous system functions (including brain functions), to explain the mechanisms of neurological disorders, and to serve as a guide to surgical intervention. Over the past century, considerable efforts have been made towards tracing the neuronal connectivity of the central nervous system. In spite of enormous progress, almost all techniques to-date are invasive and/or destructive, thus excluding them from clinical use on human subjects. Therefore, a non-invasive tractographic technique that may be directly applied to patients would be desirable.

It was recognized more than a decade ago that magnetic resonance imaging (MRI) may be used to characterize certain diffusion properties of tissues. Over the past few years, the interest in diffusion-weighted MRI has increased considerably, largely due to the discovery that diffusion imaging may be used to detect cerebral ischemia shortly after onset. This is important since therapeutic intervention using tissue perfusive agents is effective only within a narrow time window. Stimulated by the success in qualitative diffusion-weighted imaging, the interest in quantitative diffusion imaging is growing.

Published studies on quantitative diffusion imaging are primarily based on a single parameter known as the apparent diffusion coefficient (ADC). This parameter characterizes the average water mobility in tissues and may reveal microscopic tissue structural information, such as cellularity or cell membrane integrity. Although quantitative ADC maps have been useful in several applications, including characterization of tumors and evaluation of therapeutic drugs, ADC reflects only one

aspect of tissue diffusion properties. With this parameter alone, the nature of diffusion anisotropy in biological tissues is unfortunately disguised, and a wealth of tissue information is lost.

Diffusion in biological tissues is a complicated phenomenon. Depending on the tissue structures, diffusion may be spatially isotropic (such as in cerebrospinal fluid), or anisotropic (such as in white matter tracts). Diffusion anisotropy in biological tissues has been recognized for many years. Recently, a number of research groups began to study certain aspects of tissue diffusion anisotropy using MR imaging techniques. However, a robust 3D tractographic technique for routine clinical use has not been developed because of numerous technical difficulties such as insufficient contrast, low signal-to-noise ratio, problems due to patient movement, and problems due to image misregistration. It would therefore be advantageous to have the ability to generate non-invasive tractograms, exhibiting few if any technical difficulties, for routine clinical applications and for scientific and medical research.

SUMMARY OF THE INVENTION

In one respect, the invention is a method for generating a tractogram of a subject. A plurality of diffusion-weighting gradients are applied to the subject. A plurality of magnetic resonance signals arising from the application of the plurality of diffusion-weighting gradients are received. A plurality of diffusion-weighted magnetic resonance images are determined using the plurality of magnetic resonance signals. A plurality of diffusion anisotropy images are determined using the plurality of diffusion-weighted magnetic resonance images. The tractogram are generated using the plurality of diffusion anisotropy images.

In other respects, the plurality of diffusion-weighting gradients may include two or more sets of gradients, each set of gradients including a different diffusion-weighting gradient amplitude. Each set of the plurality of diffusion-weighting gradients may include six or more non-overlapping orientations, the orientations being substantially identical in each of the sets. The orientations may be evenly distributed in three dimensions. Three of the orientations may be applied along three orthogonal axes with respect to the subject and the remaining orientations may be

evenly distributed in three dimensions. One of the sets may include a diffusion-weighting gradient amplitude of about zero, and at least one other set may include a diffusion-weighting gradient that is non-zero. The one set including a diffusion-weighting gradient amplitude of about zero may include a single orientation, and the at least one other set may include six or more non-overlapping orientations. The diffusion-weighted magnetic resonance images and the anisotropy images may be three-dimensional. The diffusion-weighted magnetic resonance images and the anisotropy images may be obtained by interleaving a plurality of two-dimensional slice images. The two-dimensional slice images may be offset by a predetermined amount in a slice-selection direction. The method may also include averaging a plurality of the diffusion-weighted magnetic resonance images from repeated acquisition. Determining the plurality of diffusion anisotropy images may include determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images; determining eigenvalues of a matrix defined by the diffusion tensor elements; and determining a relative anisotropy, a fraction anisotropy, a volume ratio, an anisotropy index, or any combination thereof using the eigenvalues. The determining diffusion tensor elements may include using a least-squares algorithm. The method may also include compensating the plurality of magnetic resonance signals for eddy currents. Applying a plurality of diffusion-weighting gradients may include single-shot imaging. The single-shot imaging may include echo planar imaging, fast spin echo imaging, or any combination thereof. Applying a plurality of diffusion-weighting gradients may include multi-shot imaging. The multi-shot imaging may include echo planar imaging, fast spin echo imaging, or any combination thereof. Generating the tractogram may include using a maximum intensity projection algorithm. The tractogram may include a brain tractogram. The tractogram may include a spinal tractogram.

In another respect, the invention is a method for generating a tractogram of a subject. A first set of diffusion-weighting gradients is applied to the subject, the first set including six or more non-overlapping orientations, each gradient of the first set having a first gradient amplitude. A second set of diffusion-weighting gradients is applied to the subject, the second set including the six or more non-overlapping orientations, each gradient of the second set having a second gradient amplitude not equal to the first gradient amplitude. A plurality of magnetic resonance signals

arising from the application of the first and second sets of diffusion-weighting gradients is received. A plurality of diffusion-weighted magnetic resonance images are determined using the plurality of magnetic resonance signals. Diffusion tensor elements are determined using the plurality of diffusion-weighted magnetic resonance images. Eigenvalues of a matrix defined by the diffusion tensor elements are determined. A plurality of diffusion anisotropy images are determined using the eigenvalues. The tractogram is generated using the plurality of diffusion anisotropy images.

In other respects, the orientations may be evenly distributed in three dimensions. Three of the orientations may be applied along three orthogonal axes with respect to the subject and the remaining orientations may be evenly distributed in three dimensions. The diffusion-weighted magnetic resonance images and the anisotropy images may be three-dimensional. The diffusion-weighted magnetic resonance images and the anisotropy images may be obtained by interleaving a plurality of two-dimensional slice images. The two-dimensional slice images may be offset by a predetermined amount in a slice-selection direction. The method may also include averaging a plurality of the diffusion-weighted magnetic resonance images from repeated acquisition. Determining the plurality of diffusion anisotropy images may include determining a relative anisotropy, a fraction anisotropy, a volume ratio, an anisotropy index, or any combination thereof using the eigenvalues. Determining diffusion tensor elements may include using a least-squares algorithm. The method may also include compensating the plurality of magnetic resonance signals for eddy currents. Applying the first and second sets of diffusion-weighting gradients may include single-shot imaging. The single-shot imaging may include echo planar imaging, fast spin echo imaging, or any combination thereof. Applying the first and second sets of diffusion-weighting gradients may include multi-shot imaging. The multi-shot imaging may include echo planar imaging, fast spin echo imaging, or any combination thereof. Generating the tractogram may include using a maximum intensity projection algorithm.

In another respect, the invention is a system for generating a tractogram, including a magnetic resonance imaging device, a memory, and a microprocessor. The magnetic resonance imaging device is configured to apply to a subject two or

more sets of diffusion-weighting gradients, each set comprising six or more non-overlapping orientations and to receive a plurality of corresponding magnetic resonance signals. The memory is configured to store information corresponding to the magnetic resonance signals. The microprocessor is in communication with the memory and is configured to perform instructions including: determining a plurality of diffusion-weighted magnetic resonance images using the information corresponding to the magnetic resonance signals; determining a plurality of diffusion anisotropy images using the plurality of diffusion-weighted magnetic resonance images; and generating the tractogram using the plurality of diffusion anisotropy images.

In other respects, determining a plurality of diffusion anisotropy images may include: determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images; determining eigenvalues of a matrix defined by the diffusion tensor elements; and determining a plurality of diffusion anisotropy images using the eigenvalues. Determining diffusion tensor elements may include using a least-square algorithm. Generating the tractogram may include using a maximum intensity projection algorithm.

In another respect, the invention is a computer readable media containing program instructions for generating a tractogram. The computer readable media includes instructions for determining a plurality of diffusion-weighted magnetic resonance images using information corresponding to a plurality of magnetic resonance signals. It also includes instructions for determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images. It also includes instructions for determining eigenvalues of a matrix defined by the diffusion tensor elements. It also includes instructions for determining a plurality of diffusion anisotropy images using the eigenvalues. It also includes instructions for generating the tractogram using the plurality of diffusion anisotropy images.

As used herein, diffusion-weighting gradient means a gradient to encode diffusion information into one or more MRI signals. Diffusion tensor means a mathematical description of diffusion properties of a material, including biological tissue. Tractography means a technique to produce an image that highlights one or

more fiber tracts and suppresses background tissues. Tractogram means an image that highlights one or more fiber tracts with minimal signal from the background tissues. Diffusion anisotropy means molecular diffusion with spatially preferred directions in certain materials, including biological tissues. The indefinite articles "a" and "an" mean "one or more" when used in conjunction with the transitional phrase comprising.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to one or more of these drawings in combination with the detailed description of specific embodiments presented herein.

FIG.1 shows a process flow for generating a tractogram of a subject in accordance with the present disclosure.

FIG.2 shows a diffusion-weighted multi-shot Echo Planar Imaging (EPI) pulse sequence in accordance with the present disclosure.

FIG.3 shows a diffusion-weighted single-shot Fast Spin Echo (FSE) pulse sequence in accordance with the present disclosure.

FIG.4A shows a diffusion-weighted EPI image free of eddy currents.

FIG. 4B shows a diffusion-weighted EPI image shifted by spatially invariant eddy currents.

FIG.5A shows a diffusion-weighted EPI image that has been sheared by spatially linear eddy currents along the readout direction.

FIG.5B shows a diffusion-weighted EPI image that has been compressed by spatially linear eddy currents along the phase-encoding direction.

FIG. 6 shows a schematic diagram of a system for generating a tractogram in accordance with the present disclosure.

FIG. 7 shows different gradient orientations for n=28 in accordance with the present disclosure.

FIG. 8 shows a graph of contrast-to-noise ratio (CNR) versus b-value in accordance with the present disclosure.

FIG. 9 shows a graph of CNR versus number of gradient orientations, n, in accordance with the present disclosure.

FIG. 10 shows a diffusion-tensor image. In this image, n=6, signal averaging = 8, and b= 2500 s/mm^2 in accordance with the present disclosure.

FIG. 11 shows a diffusion-tensor image. In this image, n=55, signal averaging = 1, and b= 1000 s/mm^2 in accordance with the present disclosure.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

Understanding neuronal connectivity is essential to answering many important questions presently confronting neuroscience, neuropathology, neuro-oncology, psychiatry, clinical psychology, and various other areas. The journey to search for an *in-vivo* technique to visualize the neuronal connectivity of a living brain started more than a century ago, but it was not until recently that diffusion-weighted MR imaging began to show promising results. The present disclosure provides a number of key components crucial to developing this unrealized potential into a clinical reality. The present disclosure may be utilized to not only solve several key problems hampering diffusion tensor imaging, but also to provide scientists and clinicians with a new tool to probe neuronal connectivity *in-vivo*. Using this tool, researchers may be able to explore a number of important questions in neuroscience, such as the relationship between brain structure and function, the mechanisms of neurologic disorders, and the process of myelination. Using the same tool, clinicians may be able to obtain a wealth of new information for improved diagnosis and treatment. Additionally,

techniques disclosed herein may prove to extend the applications of magnetic resonance imaging into new, important territories.

Fiber tracts in the central nervous system include bundles of axons grouped together along certain axes. Because of this directional linkage and connectivity, water molecules diffuse more freely along the fiber tracts than along other directions. By exploiting this diffusion anisotropy at each spatial location, fiber tracts may be separated from the background tissues. This provides a basis for certain tractographic techniques disclosed herein. The present disclosure, which uses techniques that may be referred to as magnetic resonance tractography (MRT), provides for the ability to visualize three-dimensional location and orientation of fiber tracts in the central nervous system, including tracts in the brain and spine.

Molecular diffusion in anisotropic media, such as fiber tracts in the brain, may generally be characterized by a second rank tensor. Mathematically, this tensor may be expressed as a 3x3 matrix:

$$\overline{\overline{D}} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}. \qquad [1]$$

Each element in the above matrix represents a diffusion coefficient that describes the orientation-dependent diffusion process in a laboratory coordinate system defined by the x, y, and z-axes. Since the matrix is symmetric (i.e., $D_{xy} = D_{yx}$, $D_{yz} = D_{zy}$, and $D_{zx} = D_{xz}$), only six elements are required to fully describe the diffusion anisotropy at each spatial location. In contrast, diffusion in isotropic media, such as cerebrospinal fluid, may be characterized by a single diffusion coefficient D. In other words, the corresponding diffusion tensor (Equation [1]) for isotropic media would have a spherical geometry where all off-diagonal elements are zero, and the three diagonal elements are all equal to D.

To separate the fiber tracts from the rest of the tissues based on diffusion anisotropy, one embodiment of the presently disclosed tractographic technique includes steps illustrated in FIG. 1. In step 20 of general process flow 10, diffusion-

weighting gradients are applied to a subject by any one of several techniques known in the art. United States Patent No. 5,864,233, which is hereby incorporated by reference in its entirety, describes at least one technique suitable for this step. In one embodiment, the subject may be a human, but it will be understood that techniques disclosed herein apply equally well to non-human subjects. In step 30, magnetic resonance (MR) signals, arising from the subject in the presence of the diffusion-weighting gradients, are received. In step 40, diffusion-weighted MR images are reconstructed using the MR signals acquired in step 30. In step 50, diffusion anisotropy images are determined using the diffusion-weighted MR images acquired in step 40. In step 60, a tractogram is generated using the diffusion anisotropy images acquired in step 50. As illustrated, step 50 may, in one embodiment, include steps 42, 44, and 46. In step 42, diffusion tensor elements, such as those set forth in Equation [1] are determined using the diffusion-weighted MR images acquired in step 40. In step 44, eigenvalues of the tensor matrix are determined by any one of several methods known in the art, and in step 46 diffusion anisotropy is determined using those eigenvalues. The description below, directed mostly to specific embodiments of the present disclosure, more specifically explains the steps illustrated in FIG. 1.

1. Acquire a first set of raw diffusion-weighted images

Again, step 20 of FIG. 1 involves the application of diffusion-weighting gradients to a subject. According to one embodiment, a diffusion-weighting gradient $\bar{G}_{d1}$ with a fixed amplitude G_{d1} may be applied to the subject to be imaged. The diffusion-weighting gradient may change its orientation in 3D space along n non-overlapping directions (with, in one embodiment, n being no less than 6): $\bar{G}_{d11}, \bar{G}_{d12}, ..., \bar{G}_{d1n}$. At each orientation, a diffusion-weighted MR image may be obtained in 3D as illustrated in steps 30 and 40 of FIG. 1. The intensities of these images, which may be denoted as $S_{11}, S_{12}, S_{13}, ..., S_{1n}$, may be mathematically expressed as

$$S_{1j} = S_0 e^{-\int \vec{k}_{d1j} \bar{\bar{D}} \vec{k}'_{d1j} dt}, \qquad [2]$$

where S_0 is the nominal signal intensity without diffusion attenuation, j is the index of the diffusion gradient orientation (j = *1, 2, 3, ..., n*) with n greater than or equal to 6, and $\bar{k}_{d1j}$ and its transpose $\bar{k}'_{d1j}$ respectively given as:

$$\bar{k}_{d1j} = \gamma \int_0^t \bar{G}_{d1j}(t')dt' , \qquad [2a]$$

$$\bar{k}'_{d1j} = \gamma \int_0^t \bar{G}'_{d1j}(t')dt' ,$$

[2b]

$$\bar{G}_{d1j} = \begin{bmatrix} G_{d1jx} & G_{d1jy} & G_{d1jz} \end{bmatrix} = G_{d1} \begin{bmatrix} p_j & q_j & r_j \end{bmatrix}, \qquad [2c]$$

$$\bar{G}'_{d1j} = \begin{bmatrix} G_{d1jx} \\ G_{d1jy} \\ G_{d1jz} \end{bmatrix} = G_{d1} \begin{bmatrix} p_j \\ q_j \\ r_j \end{bmatrix}.$$

[2d]

In the above equations, γ is the gyromagnetic ratio, G_{d1jx}, G_{d1jy} and G_{d1jz} are the three orthogonal gradient components, respectively, and p_j, q_j and r_j are the corresponding directional cosines of $\bar{G}_{d1j}$.

2. Acquire a second set of raw diffusion-weighted images

Using the same number (n) and the same directions of the diffusion-weighing gradients as discussed above, an additional set of diffusion-weighted images may be acquired with a different diffusion-weighting gradient amplitude G_{d2}. This second data set may be denoted as $S_{21}, S_{22}, S_{23}, ..., S_{2n}$. In a case where $G_{d2} = 0$, only one single image is required since $S_{21}, S_{22}, S_{23}, ..., S_{2n}$ are the same (except for noise).

Because raw diffusion-weighted images are a major building block of MR tractography techniques disclosed herein, the technique used to acquire the raw images illustrated in steps 20 and 30 of FIG. 1 may affect the quality of the

tractograms generated in step 60 of FIG. 1. Although other imaging techniques known in the art may be used in conjunction with the present disclosure, two techniques suitable for use with the present disclosure are: echo planar imaging (EPI) and fast-spin echo (FSE). In one embodiment, EPI may be used for the brain, and FSE may be used for the spine. This distinction is primarily based on the fact that FSE may be more immune to the magnetic susceptibility variations in the spine region while EPI may give better SNR and resolution (as well as contrast) in the brain. In one embodiment, an EPI sequence such as the one illustrated in FIG. 2 may be used.

In FIG. 2, there is shown a diffusion-weighted multi-shot EPI pulse sequence. The single-shot version may be obtained by fixing the pre-phase-encoding gradient to a constant. The diffusion-weighting gradients (shaded) straddle the 180° RF pulse and their amplitude and orientation are varied throughout the acquisition. In another embodiment, an FSE sequence such as the one illustrated in FIG. 3 may be used to acquire the diffusion-weighting images.

In FIG. 3, there is shown a diffusion-weighted FSE pulse sequence. The pulse sequence may be used either in a single-shot acquisition or in a multi-shot acquisition. Diffusion-weighting gradients (shaded) are applied before and after the 180° RF pulse. The 90° pulse following the 180° pulse returns the magnetization to the longitudinal axis. Any residual magnetization on the transverse plane is crushed out by the spoiling gradient (Gsp) on the phase-encoding axis. Details of the sequence after the spoiling gradient may be found in the art, such as in D. G. Norris, P. Börnert, T. Reese, D. Leibfritz, "On the Application of Ultra-fast RARE Experiments," *Magn. Reson. Med.*, 27:142-164 (1992), which is hereby incorporated by reference in its entirety.

In one embodiment, a single-shot, multi-slice technique may be used to produce diffusion-weighted images in multiple directions (≥6) with b-values ranging from 0 to about 3000 s/mm^2. With such a technique, it is expected that one may obtain acceptable diffusion-weighted images with relatively low spatial resolution (*e.g.*, 128^2 matrix on a 24cm field-of-view for the brain with a slice thickness of about 5-7mm). In another embodiment, a multi-shot diffusion imaging techniques may be

used, which may improve the spatial resolution. With such a technique, is expected that one may obtain a spatial resolution of about 1mm for the brain and about 2mm for the spine (256x256 on 24 and 48 cm field-of-views, respectively).

Example 1 discussed below addresses the optimization of gradient orientations. In one embodiment, MRT requires six or more diffusion gradient orientations for each b-value (in the special case where b = 0, only one diffusion gradient orientation is required). Additionally, signal averaging may, in some embodiments, be necessary to improve signal-to-noise ratio. Instead of separating these two operations -- applying gradients and signal averaging -- an acquisition scheme may be utilized that achieves signal averaging by increasing the total number of gradient orientations. For example, if n gradient orientations are required and m averages are planned for each orientation, instead of treating the two operations separately, one may acquire the images with a total of $n*m$ different diffusion gradient orientations.

Another issue in diffusion gradient optimization involves how to determine the directions for a given number of gradient orientations. In one embodiment, one may evenly distribute the gradient orientations in a 3D sphere. Such a scheme may provide an equal weighting for all fiber tracts irrespective of their orientations. In another embodiment, the first three gradient orientations may be selected along the three orthogonal axes x, y and z. The remaining $n-3$ orientations may be selected with equal solid-angle weighting on the 3D sphere. An example of a this scheme for distributing the gradient orientations is given in FIG. 7 for n=28. With the benefit of the present disclosure, those having skill in the art will recognize that many other schemes to distribute the gradient orientations, and schemes with different values for n, may be employed to generate tractograms.

3. Calculate diffusion tensor maps

Again, steps 50 and 60 of FIG. 1 involve the determination of diffusion anisotropy images and the generation of a tractogram. According to one embodiment, the logarithms (I_j) of the image ratios may be taken from the corresponding image pairs acquired in the steps described above:

$$I_j = ln\left(S_{2j}/S_{1j}\right) = \int \bar{k}_{d1j} \overline{\overline{D}} \bar{k}'_{d1j} dt - \int \bar{k}_{d2j} \overline{\overline{D}} \bar{k}'_{d2j} dt \,. \qquad [3]$$

where j denotes a unique diffusion gradient orientation index from 1 to n ($j = 1, 2, 3, \ldots n$). Incorporating Eqs. [1, 2a-b] into Equation [3], one obtains:

$$I_j = (\lambda_1 - \lambda_2) \begin{bmatrix} p_j & q_j & r_j \end{bmatrix} \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix} \begin{bmatrix} p_j \\ q_j \\ r_j \end{bmatrix} , \qquad [4]$$

where λ_1 and λ_2 are constants that are proportional to the square of the diffusion-weighting gradient amplitudes, G_{d1}^2 and G_{d2}^2, respectively, and are determined by the diffusion-weighting gradient waveforms (such as position, duration and shape). The explicit expressions of λ_1 and λ_2 may be obtained by carrying out the integrals in Equation 3 above. The coefficients λ_1 and λ_2 are also known as the b-value or b-factor, which determine the degree of diffusion weighting and may influence contrast-to-noise ratio. Since $j = 1, 2, 3, \ldots, n$, Equation [4] contains n linear equations with respect to the six diffusion tensor elements. When $n=6$, the six independent tensor elements may be uniquely determined (*see* step 42 of FIG. 1). When $n>6$, the tensor elements may be unambiguously obtained using a least-squares algorithm, as is known in the art (*see* step 42 of FIG. 1).

The diffusion tensor elements obtained above are patient-orientation dependent. To obtain a set of unique diffusion anisotropy parameters independent of patient orientations, the matrix defined by Equation [1] may be mathematically manipulated. A common way, but not the only way, is to diagonalize the matrix in Equation [1] to the following form (*see* step 44 of FIG. 1):

$$\overline{\overline{D}}' = \begin{bmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{bmatrix} . \qquad [5]$$

where D_1, D_2 and D_3 are the eigenvalues. It should be noted that Equation [5] is used only to demonstrate the concept that a set of orientation-independent parameters may

be obtainable by diagonalization. Those having skill in the art will recognize that, under some circumstances, one may choose not to use the diagonalization technique due to its sensitivity to noise, as is known in the art through articles such as A.M. Ulug and P.C. van Zijl, *JMRI*, 9:804-13, 1999, which is hereby incorporated by reference in its entirety.

4. Generate tractograms

To create contrast between fiber tracts and the surrounding tissues, an anisotropy parameter, may be used to form diffusion anisotropy images as illustrated in steps 46 and 50 of FIG. 1. One or a combination of diffusion anisotropy parameters known in the art may be used in this step.

Although the diffusion tensor has only three invariants, various mathematical combinations of these invariants may yield a large number of diffusion anisotropy parameters, such as relative anisotropy (RA, Equation [12]), fractional anisotropy (FA, Equation [13]), volume ratio (VR, Equation [14]), and anisotropy index (AI, Equation [15]). Again, any one or any combination of such parameters may be used in accordance with the present disclosure.

$$RA = \frac{\sqrt{\sum_{i=1}^{3}(D_i - D_{avg})^2}}{\sqrt{3}D_{avg}}, \quad [12]$$

$$FA = \sqrt{1 - \frac{D_1D_2 + D_2D_3 + D_3D_1}{9D_{avg}^2 - 2(D_1D_2 + D_2D_3 + D_3D_1)}}, \quad [13]$$

$$VR = \frac{D_{volm}^3}{D_{avg}^3} \quad [14]$$

$$AI = 2(3D_{avg}^2 - 2D_{surf}^2 - D_{volm}^2) \quad [15]$$

where

$$D_{avg} = \frac{1}{3}(D_1 + D_2 + D_3).$$

[16]

$$D_{surf} = \frac{1}{\sqrt{3}}\sqrt{D_1 D_2 + D_2 D_3 + D_3 D_1}$$

[17]

$$D_{volm} = \sqrt[3]{D_1 D_2 D_3}\ .$$

[18]

To create a 3D diffusion anisotropy image, 3D diffusion-weighted images may be acquired directly using a 3D pulse sequence. Alternatively, multiple sets of multi-slice images may be acquired using a 2D EPI or FSE pulse sequence. The multiple 2D image sets may be offset by a predetermined amount along the slice-selection direction, and interleaved together to form a 3D image. If a 3mm slice thickness is used with a 3mm gap, a total of two interleaves with 20 slices in each set should cover an entire brain. Since a relatively long TR (3-5s) may be used in the diffusion-weighted sequences, it is expected that all 20 images in an interleave group may be acquired within a single TR. After the 3D diffusion anisotropy image is created using either a 3D or a 2D pulse sequence, tractograms may be generated using maximum intensity projection (MIP) algorithms which may project a two-dimensional plane along a number of specified directions, as is known in the art through references such as United States Patent No. 5,566,282, which is hereby incorporated by reference in its entirety. In one embodiment, an algorithm such as the one published in W. Dixon, L. Du, D. Faul, et al., "Projection angiograms of blood labeled by adiabatic fast passage", Magn. Reson. Med., 3:454-462, 1986, which is hereby incorporated by reference, may be used. The projected 2D images constitute the tractograms mentioned in step 60 of FIG. 1.

In diffusion-weighted imaging, strong diffusion-weighting gradients may induce eddy currents, which in turn produce a time-dependent perturbation magnetic field. This magnetic field may be decomposed into a spatially invariant component,

$b_0(t)$, three linear gradient components, $g_x(t)$, $g_y(t)$, and $g_z(t)$, and spatially higher-order terms (64). In the presence of the eddy-current magnetic fields, various kinds of image quality problems can be produced, as is known in the art. For example, the spatially invariant component $b_0(t)$ may cause an EPI image to shift along the phase-encoding direction (FIGS. 4A and 4B). Linear magnetic field perturbations in the readout, phase-encoding and slice-selection directions may result in image shear (FIG. 5A), compression/dilation (FIG. 5B), and reduction of image intensity, respectively. Such problems may be referred to collectively as "image misregistration," and may be addressed via methods discussed in X. Zhou, J.K. Maier, and H.G. Reynolds, "Reduction of image misregistration in diffusion-weighted EPI", *Proc. Int'l. Soc. Magn. Reson. Med. 5th Meeting*, beginning at p. 1724, Vancouver, Canada. 1997, which is hereby incorporated by reference in its entirety.

Without being bound by theory, it is expected that varying diffusion gradients may produce different eddy currents, causing inconsistent image misregistration among the raw diffusion-weighted images. This inconsistency may possibly degrade the quality and reliability of MR tractograms. Although almost all commercial scanners currently compensate for eddy currents, it has been found that the present level of eddy current compensation may not be sufficient to completely eliminate the inconsistent image misregistration problems. This problem may introduce errors in diffusion anisotropy calculations, resulting in false positives in identifying one or more fiber tracts. For at least these reasons, one may utilize any one of several methodologies known in the art to address eddy current problems such as those described in United States Patent No. 5,864,233, which has been incorporated by reference.

Turning to FIG. 6, there is shown a system 100 suitable for generating a tractogram in accordance with the present invention. In the illustrated embodiment, the system includes a magnetic resonance imaging (MRI) scanner 105, a memory 110, a network 120, a storage device 130, a microprocessor 140, a personal computer 150, a printer 160, and a hard-copy tractogram 170.

MRI scanner 105 is configured to apply diffusion-weighting gradients to a subject. Suitable devices are varied and include systems such as those disclosed in United States Patent No. 5,864,233, which has been incorporated by reference and United States Patent No. 5,923,168, which is hereby incorporated by reference in its entirety. In one embodiment, pulse sequences may be implemented on a 1.5T GE Signa Lx-NV/i scanner, which is available commercially. However, those having skill in the art will recognize that the present disclosure is in no way limited to specific types of equipment. The GE Signa scanner is equipped with a gradient system capable of producing a maximum gradient of about 40 mT/m with a slew rate of about 150 T/m/s. The gradient system is capable of producing a broad range of b-values (at least from 0 to about 3000 s/mm^2).

Memory 110 may be configured to store information corresponding to magnetic resonance signals arising from the application of diffusion-weighting gradients to the subject. In one embodiment, memory 110 may be integrated with MRI scanner 105. Any device suitable for storing data, permanently or temporarily, may be used as memory 110. For instance, random access memory, a hard drive, a tape drive, an optical drive or the like may be used. In one embodiment, a separate memory 110 may not be needed. In such an embodiment, MRI scanner 105 may directly transfer information to a device suitable for making one or more calculations on-the-fly, without need for specific storage of that information.

Shown in FIG. 6 is network 120. Network 120 is illustrated to emphasize that MRI scanner 105 and memory 110 may be remotely connected to a calculation device, such as personal computer 150. In fact, MRI scanner 105 and memory 110 (or any equipment that may transfer information) may be remotely connected through a network or other suitable means. Network 120 may be any one of various types of networks. In one embodiment, network 120 may be the Internet. In other embodiments, network 120 may be a Local Area Network (LAN), a Wide Area Network (WAN), an intranet, or the like. In one embodiment, network 120 may not be needed. In such an embodiment, one or more pieces of equipment may be coupled directly.

Storage device 130 illustrates that system 100 may employ more than one memory storage for information. In the illustrated embodiment, information from MRI scanner 105 is transferred to memory 110. The information may then be transferred over network 120 to storage device 130 so that a calculation device, such as personal computer 150, may access that information. In one embodiment, storage device 130 may be an external hard drive. In another embodiment, storage device 130 may be an internal hard drive of personal computer 150. In yet other embodiments, storage device 130 may be random access memory, an optical drive, a tape drive, a floppy drive, or the like. In one embodiment, storage device 130 may not be needed. In such an embodiment, information may be transferred from MRI scanner 105 directly to personal computer 150, or it may be transferred from MRI scanner 105 to memory 110 to personal computer 150.

Microprocessor 140 is configured to perform the instructions disclosed herein to convert information from MR device 110 into tractogram 170. Specifically, microprocessor 140 may be configured to determine a plurality of diffusion-weighted resonance images using signals from MR device 110, determine a plurality of diffusion anisotropy images using those images, and generate tractogram 170 using those anisotropy images. More generally, microprocessor 140 may be instructed to perform any one or combination of operations discussed in FIG. 1 and throughout this description. In the illustrated embodiment, microprocessor 140 is the Central Processing Unit (CPU) of personal computer 150. In other embodiments, microprocessor 140 may be the processing unit of any number of other calculating devices, such as but not limited to, a hand-held computer, a laptop computer, a personal digital assistant, or the like.

In one embodiment, software suitable to provide instructions to microprocessor 140 may be used. Specifically software may be used to perform any one or combination of steps depicted in FIG. 1 and described throughout this specification. More specifically, software may be utilized that includes instructions for determining a plurality of diffusion-weighted magnetic resonance images using information from MRI scanner 105 following application of diffusion gradients to a subject. The software may also include instructions for determining diffusion tensor elements as discussed herein and for determining eigenvalues for a matrix defined by

those elements. The software may include instructions for determining a plurality of diffusion anisotropy images as discussed herein and may correspondingly produce tractogram 170. With the benefit of the present disclosure, and especially the equations contained herein, one of skill in the art may implement suitable software in one of many different ways. In one embodiment, a program may be written in a language such as C++, Fortran, or Visual Basic. In other embodiments, a language specifically designed to interface with MRI scanner 105 may be utilized. In still other embodiments, commercially available mathematic processing software such as MATHEMATICA and MatLab may be instructed to carry out any one or combination of instructions disclosed in this specification. In one embodiment, all image processing software may be written in C or C++ as separate modules to an existing software package such as FuncTool (GE Medical Systems, Milwaukee, Wisconsin). In one embodiment, image visualization software may be developed using the Visualization Toolkit (Prentice Hall, Upper Saddle River, NJ). To display tractogram 170, any one of several appropriate graphical programs may be used, as is known in the art. To visualize the tractograms and use them for surgical planning and radiologic evaluation, the pre-calculated tractograms may be included in a cine loop and presented as a movie, as is known in the art. The tractograms may also be displayed, in conjunction with high-resolution anatomic images, in any arbitrary orientations and view angles.

Personal computer 160 may be any device suitable for interfacing with microprocessor 140. Again, it may include but is not limited to personal computers, hand-held computers, laptop computers, personal digital assistants, and the like. In one embodiment, diffusion anisotropy image calculations, 3Dimage synthesis, and tractogram generation may all be performed on an SGI Indigo-2 Workstation (Silicon Graphics, Inc., Mountain View, CA) accessed remotely through a desktop personal computer.

Printer 160 is illustrated in FIG. 6 to demonstrate that tractogram 170 may be presented in various forms. It may be printed, viewed directly on a monitor, viewed as a movie, or by any other means suitable to convey the tractogram information to a user.

The following examples are included to demonstrate specific embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute specific modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLE 1

In Diffusion-Tensor MRI, contrast between fiber tracts and surrounding tissues arises from diffusion anisotropy, calculated from a set of diffusion-weighted images acquired with different b-values and diffusion-gradient orientations. An optimal combination of these parameters is desired for a given acquisition time to maximize image quality. In this example, different b-values and number of gradient orientations (n) are investigated on normal human volunteers. Image quality was quantitatively analyzed in terms of contrast ratio (CR) and contrast-to-noise ratio (CNR) between major tracts and surrounding tissue.

To implement the study, a diffusion-tensor pulse sequence, which was a variation of a single-shot EPI sequence, was used. This sequence allows multiple diffusion-gradient orientations to be used in a single acquisition. Raw diffusion-weighted images were acquired from human subjects on a 1.5 T GE Signa Lx-NV/i scanner. The acquisition parameters were TE = 77 ms, TR = 4 sec, matrix = 128^2, FOV = 24 cm, and slice thickness = 5 mm, with varying b-values and multiple n as discussed below. The diffusion images were processed with GE's FuncTool Analysis package, using singular-value decomposition to calculate the diffusion tensor elements and generate the diffusion anisotropy maps.

The lowest n used in this study was 6, the minimum needed to determine the diffusion tensor elements. Eight signal averages (8 NEX) were required to achieve sufficient signal-to-noise ratio for evaluation, leading to a total scan time of ~4 minutes (including acquisition of a base image with b = 0). Data sets with larger n

were acquired for comparison, with correspondingly decreased number of averages, chosen to keep acquisition time constant at 4 minutes. An iterative algorithm was used to calculate the orientations, (θ,ϕ) weighted equally by solid angle. A representative set ($n = 28$) is shown in FIG. 7.

The b-value was varied from 500 to 3000 s/mm^2 in 250 s/mm^2 increments for $n = 6$ (8 NEX) and 55 (1 NEX). For n = 9, 14, and 28, a smaller range of b-values (1250 to 1750 s/mm^2) was selected with the corresponding averages (6, 4, and 2 NEX, respectively) chosen to normalize the acquisition times.

CR and CNR were computed for several regions of interest: splenium, left/rightcorticospinal tracts, and left/right arcuate fasciculus. Gray matter without tracts in the frontal lobe was used as a contrast reference.

The relationship between CNR and b-value at two different n (6 and 55) are summarized in FIG. 8, with a polynomial fit to illustrate the trend. The experimental data suggest that increasing n may lower the optimal b-value required for maximum CNR. For n = 6 (8 NEX), the peak occurred at ~2500 s/mm^2, whereas for n = 55 (1 NEX) the optimum was between 750 and 1250 s/mm^2.

The dependence of maximum CNR on n is given in FIG. 9. The results broadly suggest that CNR may be higher at larger n. This implies that increasing n may be more effective than signal averaging at reducing noise and preserving contrast. Two relative diffusion anisotropy images are compared in FIG. 10 and FIG. 11. FIG. 10 resulted from n=6, signal averaging = 8, and b= 2500 s/mm^2. FIG. 11 resulted from n=55, signal averaging = 1, and b= 1000 s/mm^2 in accordance with the present disclosure.

EXAMPLE 2

Diffusion tensor imaging (DTI) may provide a wealth of information on molecular diffusion in biological tissues. One application is to visualize the white-matter tracts using diffusion anisotropy maps. Knowledge of the white-matter tracts

is important in pre-surgical planning and post-surgical assessment for patients with brain lesions. For this purpose, the clinical applicability of a magnetic resonance tractography technique based on DTI has been evaluated.

A total of 12 patients with primary (9) and metastatic (3) brain tumors were enrolled in this study. Patients were scanned one day prior to the operation for surgical planning and soon after the tumor resection for post-surgical evaluation.

The DTI pulse sequence used in this study was modified from a commercial diffusion-weighted, single-shot echo planar imaging (EPI) sequence. This sequence is the single-shot version of the sequence shown in FIG. 2. The sequence is capable of re-orienting the diffusion gradient in a number of pre-determined directions (>6). In the pulse sequence, the maximum available gradient (40mT/m) was used to achieve the shortest possible echo time. To address image misregistration problems induced by eddy currents, a correction mechanism as disclosed herein was included in the sequence. For signal-to-noise ratio (SNR) improvement, the sequence employed magnitude averaging to avoid the phase inconsistency among the individual diffusion images.

All images were acquired on a 1.5T GE Signa Lx-NV/i scanner (Milwaukee, WI) equipped with a high performance gradient assembly (amplitude = 40mT/m, slew-rate = 150T/m/s). A set of n diffusion-weighted images (I_1, I_2, ... I_n), each having a distinct diffusion-gradient orientation, was acquired using the DTI pulse sequence at a fixed b-value. An additional image (I_0), known as the base image, was also obtained using the same DTI sequence with zero diffusion gradient. The acquisition parameters were: TR=4s, TE=77ms, matrix=128^2, b=1576s/mm^2, n=6-28, NEX=8-2, FOV=24cm, slice thickness=5mm, and gap=4mm. To reformat the 2D multiple slices to 3D without gaps, three acquisitions, each with a slice offset of 3mm, were interleaved, resulting in a total of 39-45 slices covering the entire brain.

To obtain the diffusion tensor elements, a least-squares algorithm was employed in solving the following equation:

$$\ln(I_0 / I_j) = b \begin{bmatrix} p_j & q_j & r_j \end{bmatrix} \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix} \begin{bmatrix} p_j \\ q_j \\ r_j \end{bmatrix}$$

[19]

where b is the b-value, (p_j, q_j, r_j) is the directional cosines of the jth diffusion gradient, and $j=1, 2, \ldots n$. The diffusion tensor elements were then converted to relative diffusion anisotropy (RDA) maps. All calculations were carried out using software developed within FuncTool (GE Medical Systems, Milwaukee, WI) as discussed herein. The 2D RDA maps from all the slices were reformatted to 3D and projected within a slab (9-20mm) using a maximum intensity projection (MIP) algorithm. The MIP image constitutes an MR tractogram.

In the tractograms from all the patients, major white-matter tracts such as arcuate fasciculus, splenium, corticospinal tracts were clearly visualized with contrast-to-noise ratios exceeding 9.0. In two patients, finer structures including optical tracts and fornix were also visible. Prior to the surgery, compression of various tracts caused by the tumor masses was observed in eleven patients. Displacements of the tracts correlated well with the patients' neurological dysfunction. In the remaining one patient, the tractograms revealed that the arcuate fasciculus was profoundly disrupted by a large tumor mass (~10cm). This anatomic finding was in agreement with the patient's expressive and receptive speech problems. In one patient, restoration of the left arcuate fasciculus to the normal position was seen only two weeks after the surgery.

All of the methods, systems, and apparatus disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the techniques of this invention have been described in terms of specific embodiments, it will be apparent to those of skill in the art that variations may be applied to the disclosed methodologies and in the steps of the method described herein without departing from the concept, spirit and scope of the invention.

REFERENCES

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14. N. Makris, A.J. Worth, A.G. Sorensen, G.M. Papadimitrious, *et al.*, "Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging", *Ann. Neurol.*, 42:951-962, 1997.

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WHAT IS CLAIMED IS:

1. A method for generating a tractogram of a subject, comprising:

applying a plurality of diffusion-weighting gradients to the subject;

receiving a plurality of magnetic resonance signals arising from the application of the plurality of diffusion-weighting gradients;

determining a plurality of diffusion-weighted magnetic resonance images using the plurality of magnetic resonance signals;

determining a plurality of diffusion anisotropy images using the plurality of diffusion-weighted magnetic resonance images; and

generating the tractogram using the plurality of diffusion anisotropy images.

2. The method of claim 1, wherein the plurality of diffusion-weighting gradients comprise two or more sets of gradients, each set of gradients comprising a different diffusion-weighting gradient amplitude.

3. The method of claim 2, wherein each set of the plurality of diffusion-weighting gradients comprise six or more non-overlapping orientations, the orientations being substantially identical in each of the sets.

4. The method of claim 3, wherein the orientations are evenly distributed in three dimensions.

5. The method of claim 3, wherein three of the orientations are applied along three orthogonal axes with respect to the subject and the remaining orientations are evenly distributed in three dimensions.

6. The method of claim 2, wherein one of the sets includes a diffusion-weighting gradient amplitude of about zero, and wherein at least one other set includes a diffusion-weighting gradient that is non-zero.

7. The method of claim 6, wherein the one set including a diffusion-weighting gradient amplitude of about zero includes a single orientation, and wherein the at least one other set includes six or more non-overlapping orientations.

8. The method of claim 1, wherein the diffusion-weighted magnetic resonance images and the anisotropy images are three-dimensional.

9. The method of claim 8, wherein the diffusion-weighted magnetic resonance images and the anisotropy images are obtained by interleaving a plurality of two-dimensional slice images.

10. The method of claim 9, wherein the two-dimensional slice images are offset by a predetermined amount in a slice-selection direction.

11. The method of claim 1, further comprising averaging a plurality of the diffusion-weighted magnetic resonance images from repeated acquisition.

12. The method of claim 1, wherein determining the plurality of diffusion anisotropy images comprises:

determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images;

determining eigenvalues of a matrix defined by the diffusion tensor elements; and

determining a relative anisotropy, a fraction anisotropy, a volume ratio, an anisotropy index, or any combination thereof using the eigenvalues.

13. The method of claim 12, wherein the determining diffusion tensor elements comprises using a least-squares algorithm.

14. The method of claim 1, further comprising compensating the plurality of magnetic resonance signals for eddy currents.

15. The method of claim 1, wherein applying a plurality of diffusion-weighting gradients comprises single-shot imaging.

16. The method of claim 15, wherein the single-shot imaging comprises echo planar imaging, fast spin echo imaging, or any combination thereof.

17. The method of claim 1, wherein applying a plurality of diffusion-weighting gradients comprises multi-shot imaging.

18. The method of claim 17, wherein the multi-shot imaging comprises echo planar imaging, fast spin echo imaging, or any combination thereof.

19. The method of claim 1, wherein generating the tractogram comprises using a maximum intensity projection algorithm.

20. The method of claim 1, wherein the tractogram comprises a brain tractogram.

21. The method of claim 1, wherein the tractogram comprises a spinal tractogram.

22. A method for generating a tractogram of a subject, comprising:

applying a first set of diffusion-weighting gradients to the subject, the first set comprising six or more non-overlapping orientations, each gradient of the first set having a first gradient amplitude

applying a second set of diffusion-weighting gradients to the subject, the second set comprising the six or more non-overlapping orientations, each gradient of the second set having a second gradient amplitude not equal to the first gradient amplitude;

receiving a plurality of magnetic resonance signals arising from the application of the first and second sets of diffusion-weighting gradients;

determining a plurality of diffusion-weighted magnetic resonance images using the plurality of magnetic resonance signals;

determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images;

determining eigenvalues of a matrix defined by the diffusion tensor elements;

determining a plurality of diffusion anisotropy images using the eigenvalues; and

generating the tractogram using the plurality of diffusion anisotropy images.

23. The method of claim 22, wherein the orientations are evenly distributed in three dimensions.

24. The method of claim 22, wherein three of the orientations are applied along three orthogonal axes with respect to the subject and the remaining orientations are evenly distributed in three dimensions.

25. The method of claim 22, wherein the diffusion-weighted magnetic resonance images and the anisotropy images are three-dimensional.

26. The method of claim 25, wherein the diffusion-weighted magnetic resonance images and the anisotropy images are obtained by interleaving a plurality of two-dimensional slice images.

27. The method of claim 26, wherein the two-dimensional slice images are offset by a predetermined amount in a slice-selection direction.

28. The method of claim 22, further comprising averaging a plurality of the diffusion-weighted magnetic resonance images from repeated acquisition.

29. The method of claim 22, wherein the determining the plurality of diffusion anisotropy images comprises determining a relative anisotropy, a fraction anisotropy, a volume ratio, an anisotropy index, or any combination thereof using the eigenvalues.

30. The method of claim 22, wherein the determining diffusion tensor elements comprises using a least-squares algorithm.

31. The method of claim 22, further comprising compensating the plurality of magnetic resonance signals for eddy currents.

32. The method of claim 22, wherein applying the first and second sets of diffusion-weighting gradients comprises single-shot imaging.

33. The method of claim 32, wherein the single-shot imaging comprises echo planar imaging, fast spin echo imaging, or any combination thereof.

34. The method of claim 22, wherein applying the first and second sets of diffusion-weighting gradients comprises multi-shot imaging.

35. The method of claim 34, wherein the multi-shot imaging comprises echo planar imaging, fast spin echo imaging, or any combination thereof.

36. The method of claim 22, wherein generating the tractogram comprises using a maximum intensity projection algorithm.

37. A system for generating a tractogram, comprising:

a magnetic resonance imaging device configured to apply to a subject two or more sets of diffusion-weighting gradients, each set comprising six or more non-overlapping orientations and to receive a plurality of corresponding magnetic resonance signals;

a memory configured to store information corresponding to the magnetic resonance signals;

a microprocessor in communication with the memory and configured to perform instructions including:

determining a plurality of diffusion-weighted magnetic resonance images using the information corresponding to the magnetic resonance signals;

determining a plurality of diffusion anisotropy images using the plurality of diffusion-weighted magnetic resonance images; and

generating the tractogram using the plurality of diffusion anisotropy images.

38. The system of claim 37, wherein the determining a plurality of diffusion anisotropy images comprises:

determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images;

determining eigenvalues of a matrix defined by the diffusion tensor elements; and

determining a plurality of diffusion anisotropy images using the eigenvalues.

39. The system of claim 38, wherein the determining diffusion tensor elements comprises using a least-square algorithm.

40. The system of claim 38, wherein generating the tractogram comprises using a maximum intensity projection algorithm.

41. A computer readable media containing program instructions for generating a tractogram, the computer readable media comprising:

instructions for determining a plurality of diffusion-weighted magnetic resonance images using information corresponding to a plurality of magnetic resonance signals;

instructions for determining diffusion tensor elements using the plurality of diffusion-weighted magnetic resonance images;

instructions for determining eigenvalues of a matrix defined by the diffusion tensor elements;

instructions for determining a plurality of diffusion anisotropy images using the eigenvalues; and

instructions for generating the tractogram using the plurality of diffusion anisotropy images.

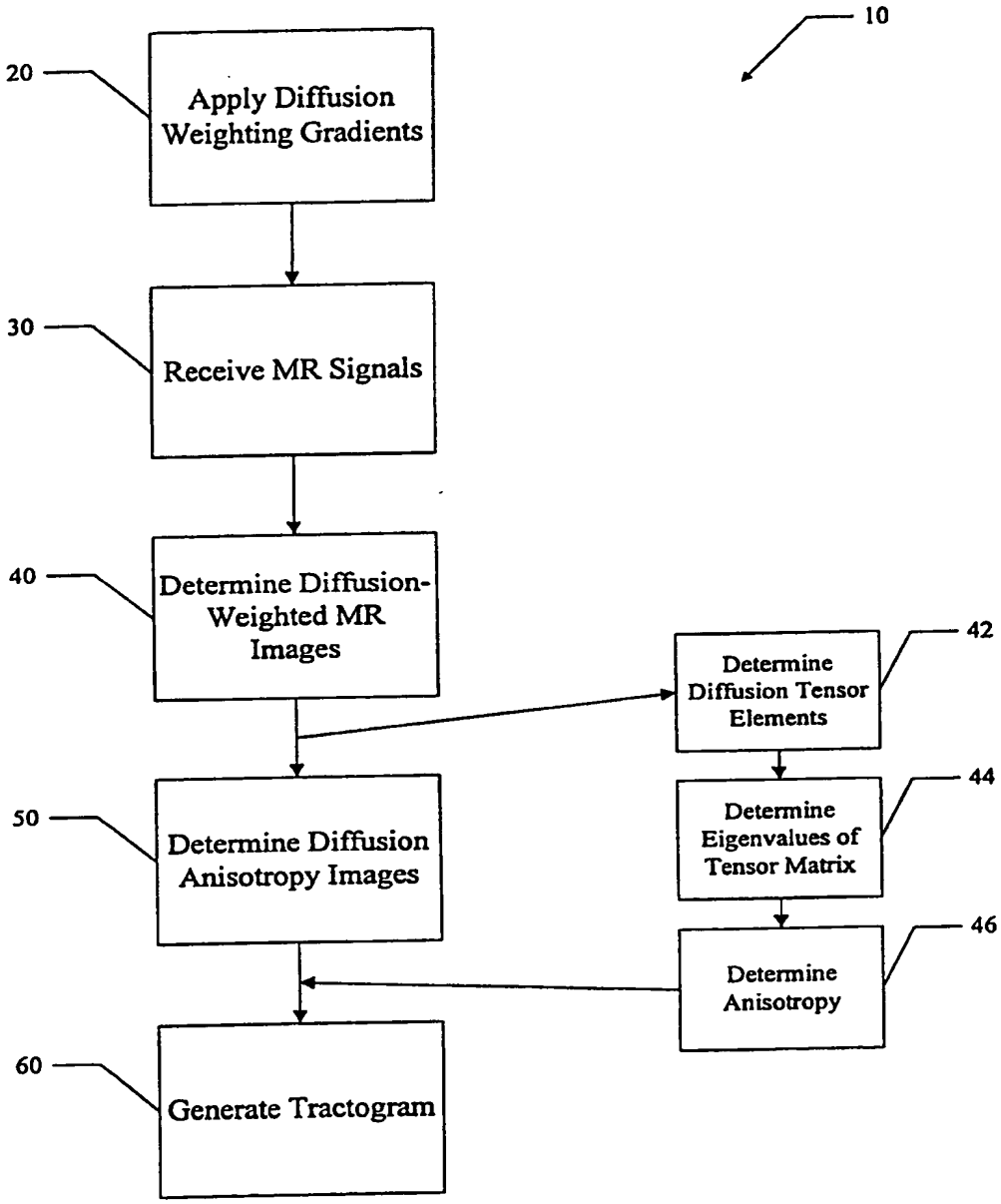

10
20
Apply Diffusion Weighting Gradients
30
Receive MR Signals
40
Determine Diffusion-Weighted MR Images
42
Determine Diffusion Tensor Elements
44
Determine Eigenvalues of Tensor Matrix
46
Determine Anisotropy
50
Determine Diffusion Anisotropy Images
60
Generate Tractogram

FIG. 1

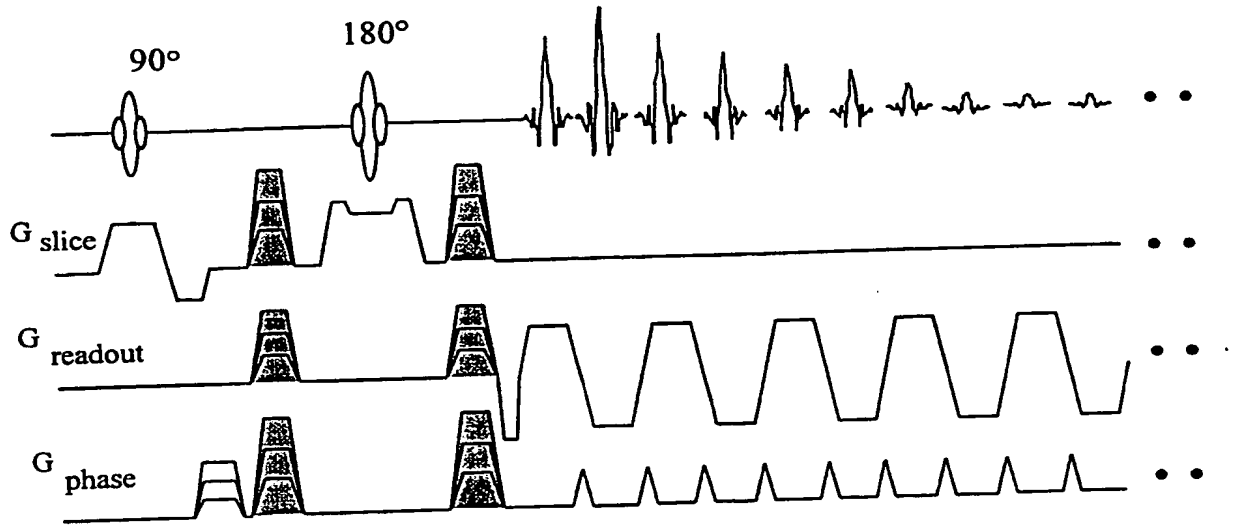


FIG. 2

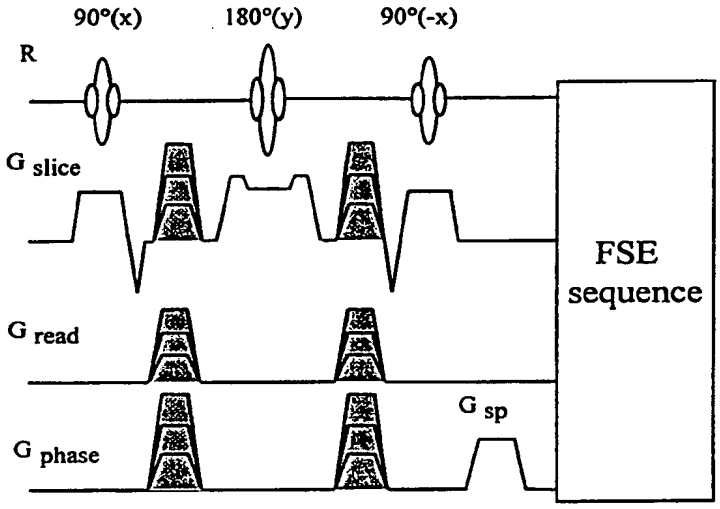


FIG. 3

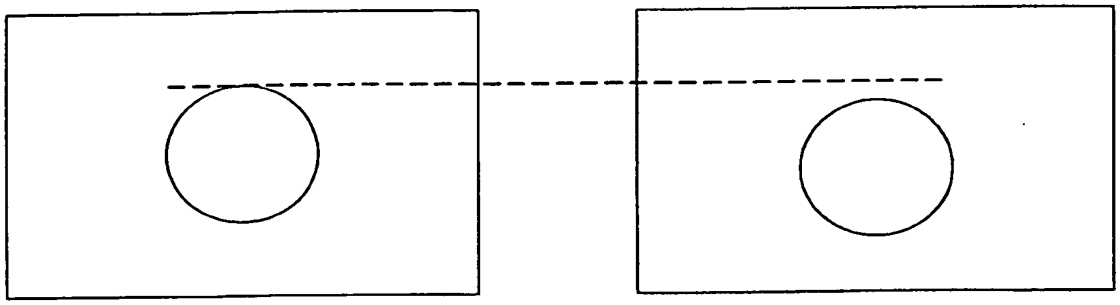


FIG. 4A FIG. 4B

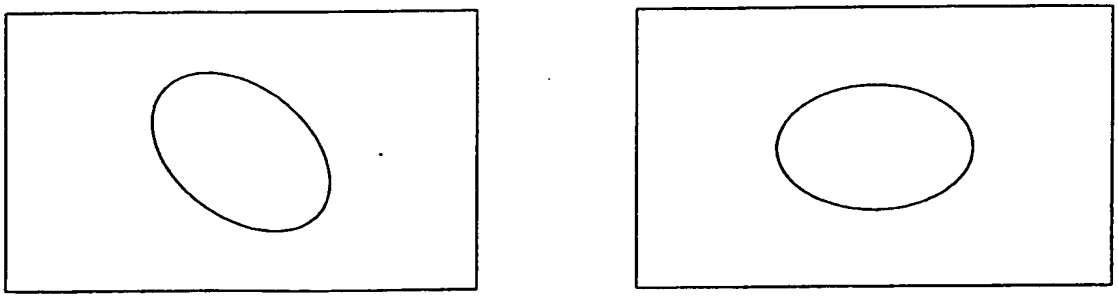


FIG. 5A FIG. 5B

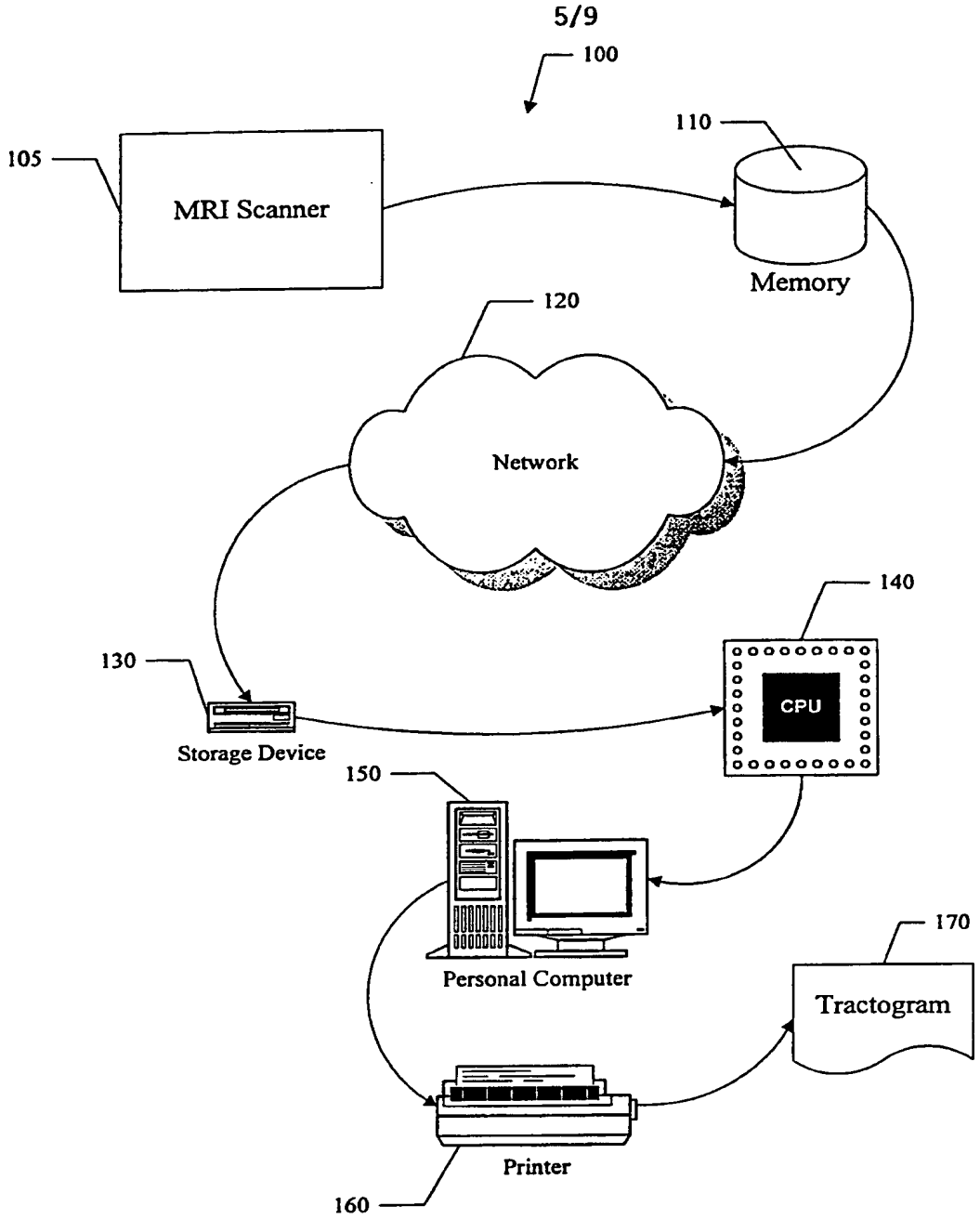

100
105
MRI Scanner
110
Memory
120
Network
130
Storage Device
140
CPU
150
Personal Computer
160
Printer
170
Tractogram

FIG. 6

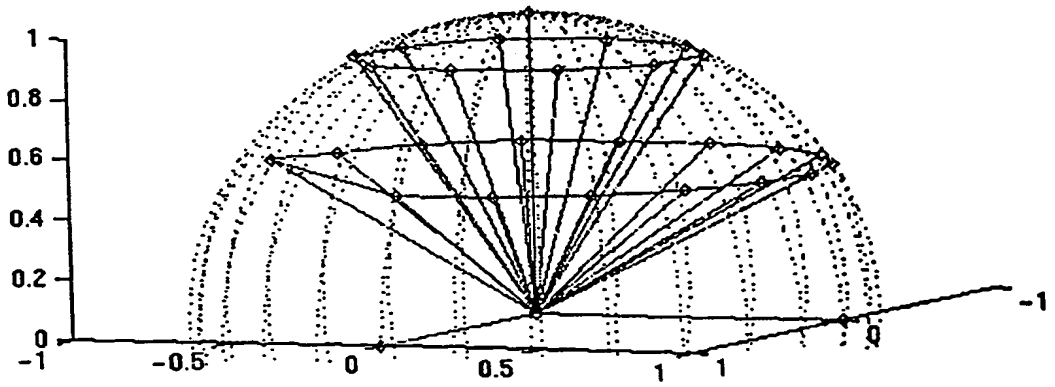


FIG. 7

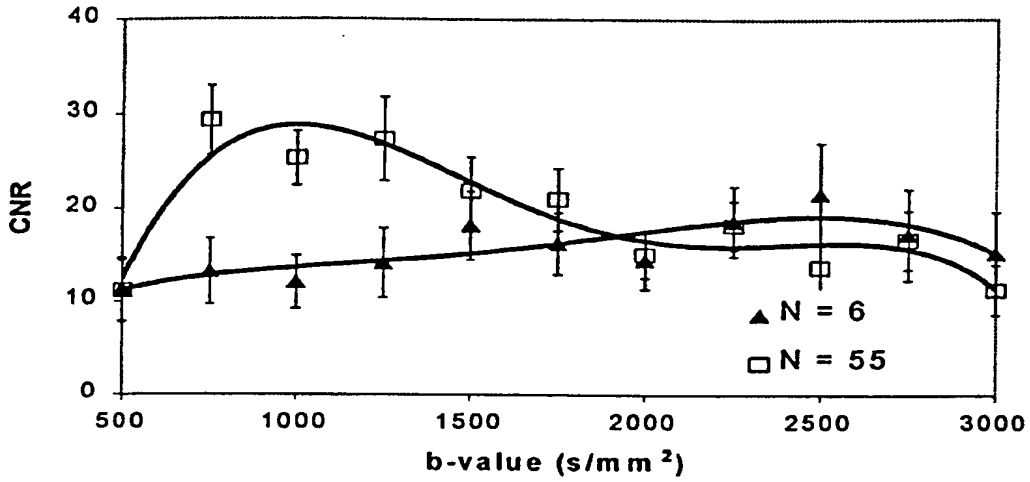

40
30
20
10
0
CNR
500
1000
1500
2000
2500
3000
b-value (s/mm²)
N = 6
N = 55

FIG. 8

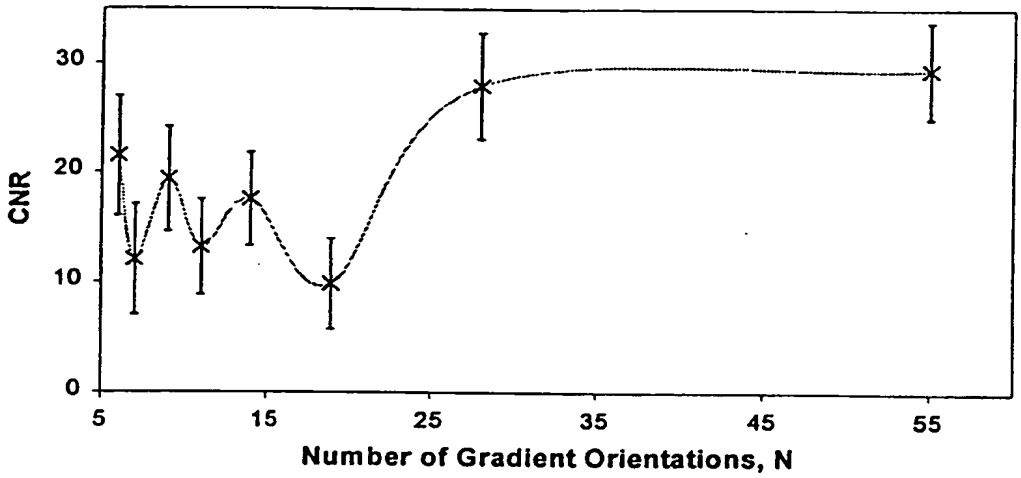
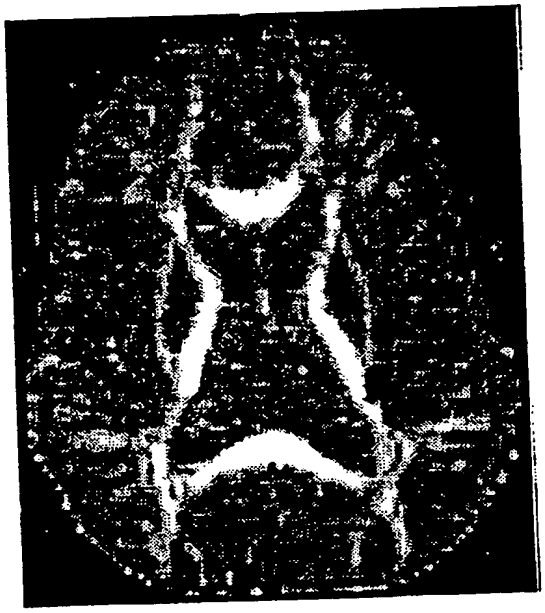
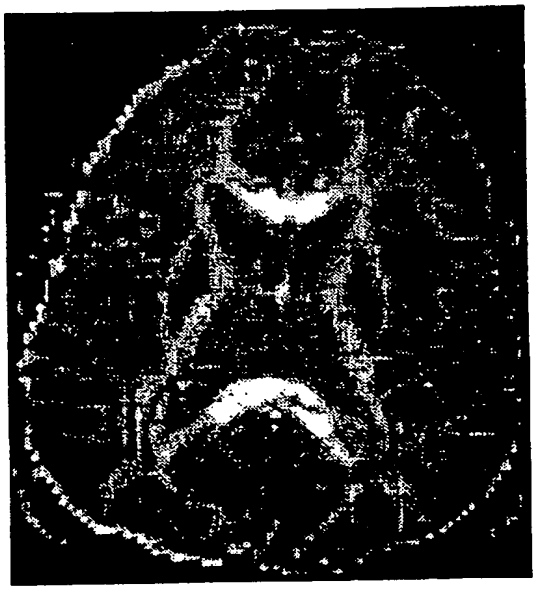

CNR
30
20
10
0
5
15
25
35
45
55
Number of Gradient Orientations, N

FIG. 9



F16. 10



F16. 11

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/US 00/32358

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01R33/563

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EPO-Internal, INSPEC, SCISEARCH, MEDLINE, COMPENDEX, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE JICST-EPLUS 'Online! Japan Science and Tech Corp (JST); KINOSADA YASUTOMI ET AL.: "MR Tractography. Visualization of Structure of Nerve Fiber System from Diffusion Weighted Images with Maximum Intensity Projection Method" XP002162558 * abstract * & NIPPON ACTA RADIOLOGICA, vol. 53, no. 2, 1993, pages 171-179, --- -/--	1-21, 37-41
A		22-36

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2001	26/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skalla, J

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/32358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	P J BASSER ET AL: "A Simplified Method to Measure the Diffusion Tensor from Seven MR Images" MAGNETIC RESONANCE IN MEDICINE,ACADEMIC PRESS, DULUTH, MN,US, vol. 39, 1998, pages 928-934, XP002145650 ISSN: 0740-3194 * see the whole document *	1-21, 37-41
A	---	22-36
Y	JONES D.K. ET AL.: "An Optimal Strategy for Precise Determination of the Diffusion Tensor" PROCEEDINGS OF THE INTERNATIONAL SOCIETY FOR MAGNETIC RESONANCE IN MEDICINE, vol. 3, 22 May 1999 (1999-05-22), page 1793 XP002162420 Philadelphia, USA * see the whole document *	5

Y	BASSER P J ET AL: "MICROSTRUCTURAL AND PHYSIOLOGICAL FEATURES OF TISSUES ELUCIDATED BYQUANTITATIVE-DIFFUSION-TENSOR MRI" JOURNAL OF MAGNETIC RESONANCE. SERIES B,US,ACADEMIC PRESS, ORLANDO, FL, vol. 111, no. 3, 1 June 1996 (1996-06-01), pages 209-219, XP000626666 ISSN: 1064-1866 * see the whole document *	12

Y	ZHOU X. ET AL.: "Reduction of Image Misregistration in Diffusion-Weighted EPI" PROCEEDINGS OF THE INTERNATIONAL SOCIETY FOR MAGNETIC RESONANCE IN MEDICINE, vol. 3, 12 April 1997 (1997-04-12), page 1724 XP002162421 Vancouver, Canada cited in the application * see the whole document *	14

A	MAKRIS N ET AL: "Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging." ANNALS OF NEUROLOGY, vol. 42, no. 6, December 1997 (1997-12), pages 951-962, XP000986335 ISSN: 0364-5134 cited in the application * see the whole document *	1-41

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INTERNATIONAL SEARCH REPORT

Inter .onal Application No
PCT/US 00/32358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PIERPAOLI C ET AL: "Toward a quantitative assessment of diffusion anisotropy" MAGNETIC RESONANCE IN MEDICINE, DEC. 1996, WILLIAMS & WILKINS, USA, vol. 36, no. 6, pages 893-906, XP002162422 ISSN: 0740-3194 * see the whole document *	1-41
A	LORI N.F. ET AL.: "Tracking Neuronal Fibers in the Living Human Brain with Diffusion MRI" PROCEEDINGS OF THE INTERNATIONAL SOCIETY FOR MAGNETIC RESONANCE IN MEDICINE, vol. 1, 22 May 1999 (1999-05-22), page 324 XP002162423 Philadelphia, USA * see the whole document *	

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